

PrEP: The Other Pill for Women

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LEARNING OBJECTIVES

1. Describe the evidence for oral HIV pre-exposure prophylaxis's (PrEP) efficacy in women
2. Apply clinical guidance to identify women with indications for oral PrEP
3. Gain insight into prescribing oral PrEP including unique considerations for women

Presentation Roadmap

- Epidemiology of HIV in U.S. women
- PrEP and the evidence for its efficacy in women
- PrEP and reproductive health
- PrEP eligibility assessment and monitoring



Clinical vignette

- Karen is a 30 year-old Black cisgender woman who presents for a routine annual visit
- Treated for a Chlamydia infection four months ago at a clinic
- Struggling to pay bills and sometimes exchanges sex for money with two of her old boyfriends
- **You wonder about her risk of future STIs especially HIV...**



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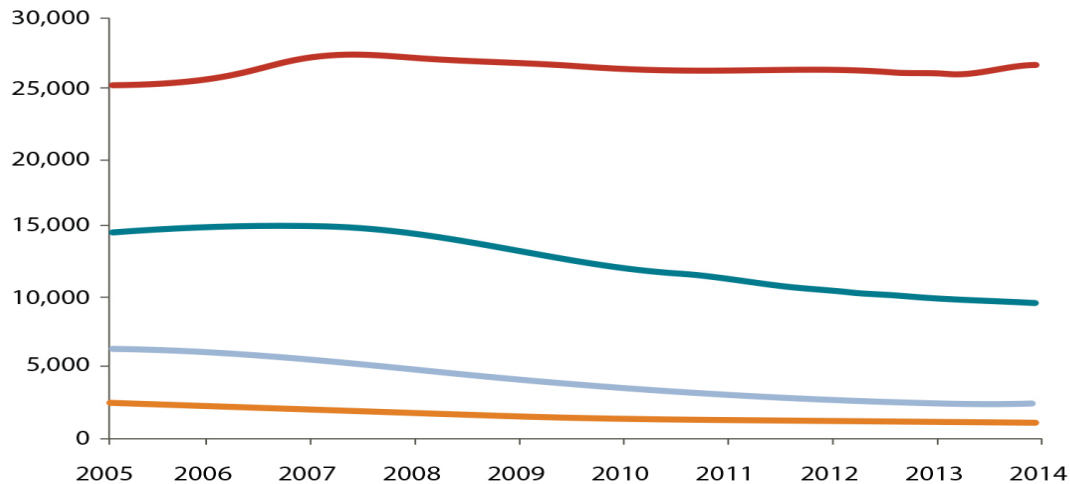


Trends in new HIV diagnoses in the U.S.

HIV Diagnoses by Transmission Category, 2005-2014

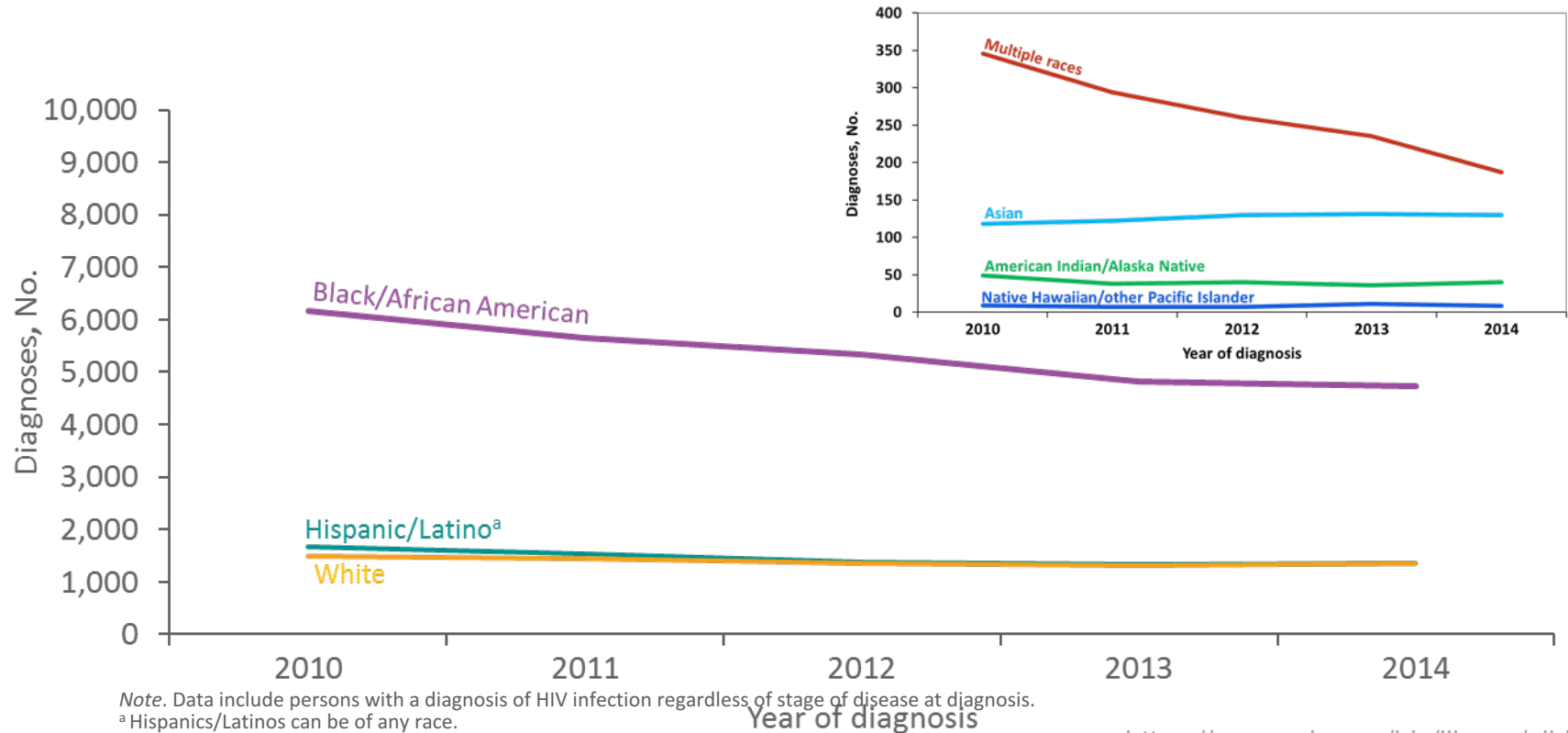
- Heterosexuals
- PWID
- MSM
- MSM/PWID

- Overall decline by 19% 2005-2014
- 48,795 to 39,718 per year
- Decreased 40% among women

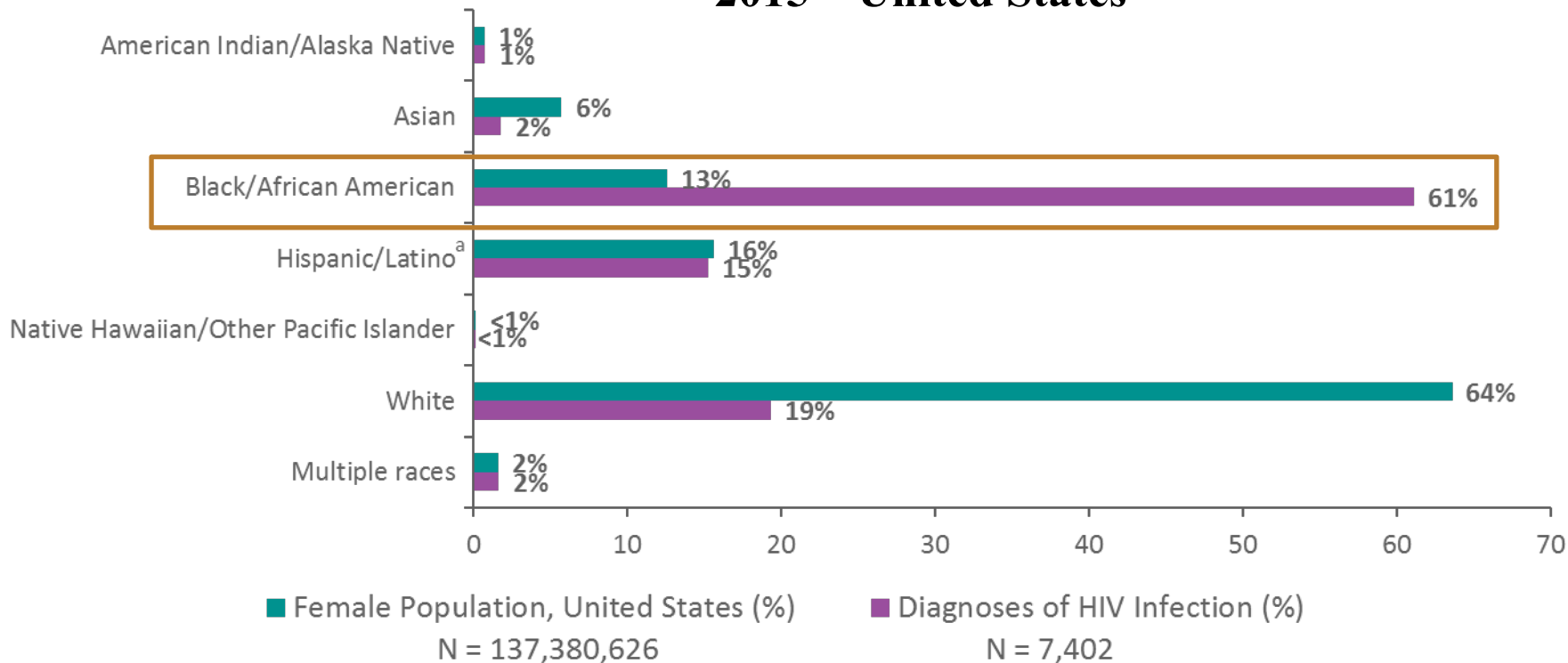


Source: Centers for Disease Control and Prevention

Diagnoses of HIV Infection among Female Adults and Adolescents, by Race/Ethnicity, 2010–2014, United States and 6 Dependent Areas



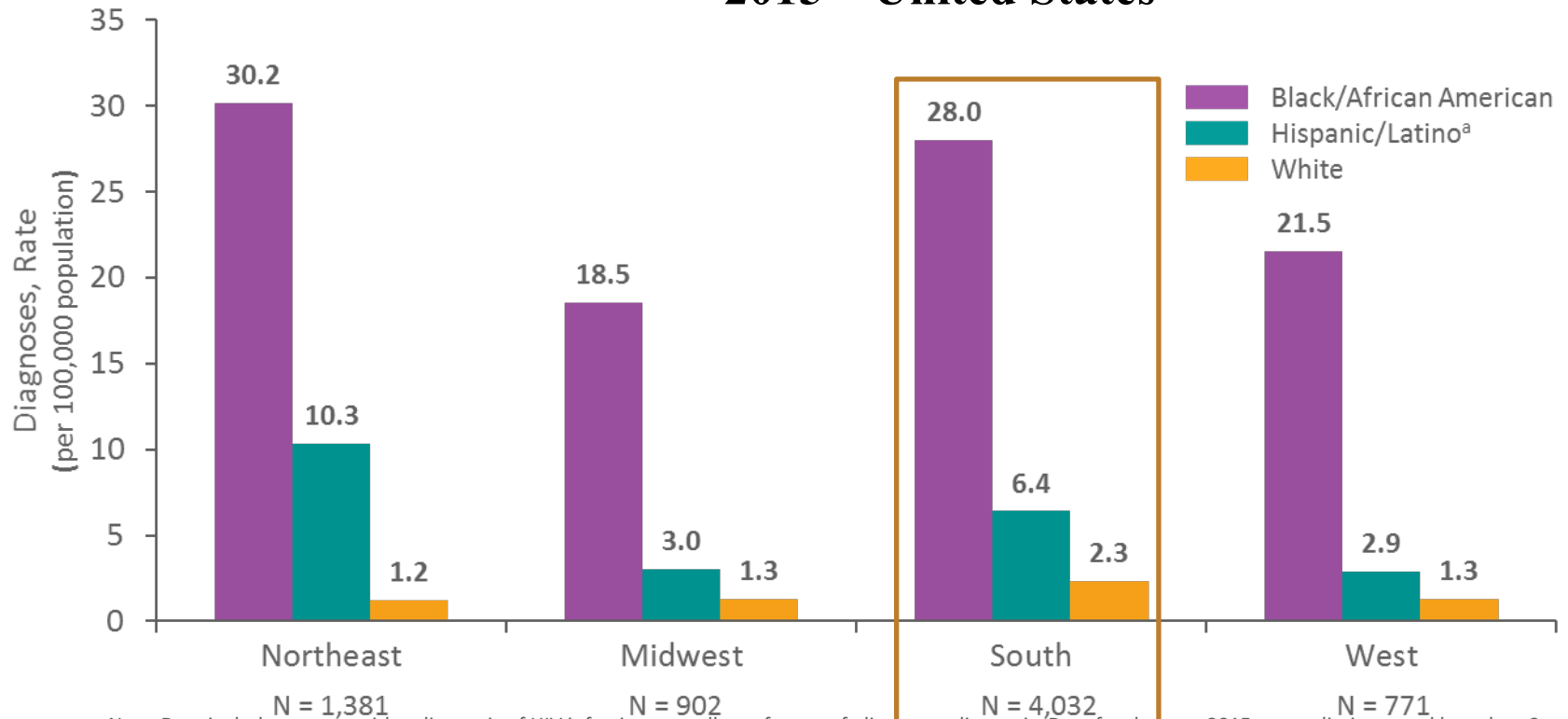
Diagnoses of HIV Infection and Population among Female Adults and Adolescents, by Race/Ethnicity, 2015—United States



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay.

^a Hispanics/Latinos can be of any race.

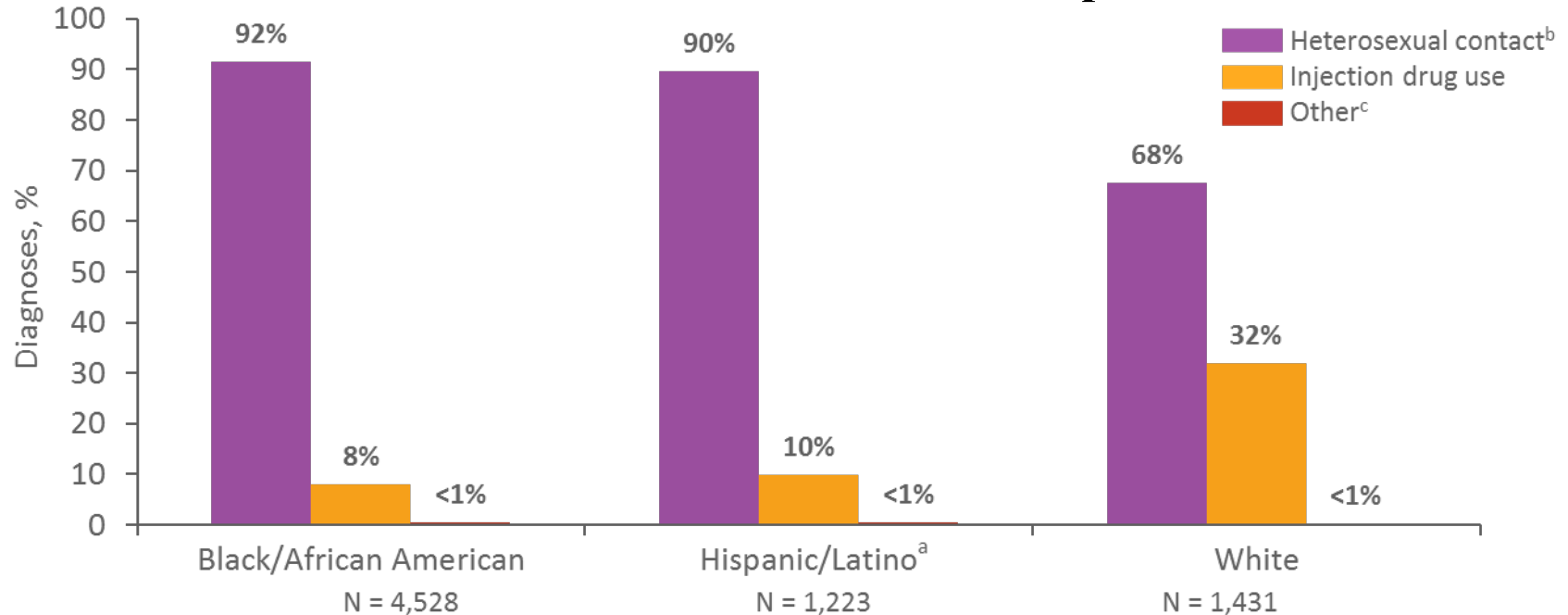
Diagnoses of HIV Infection among Female Adults and Adolescents by Region and Race/Ethnicity, 2015—United States



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Diagnoses of HIV Infection among Female Adults and Adolescents, by Race/Ethnicity and Transmission Category, 2015—United States and 6 Dependent Areas



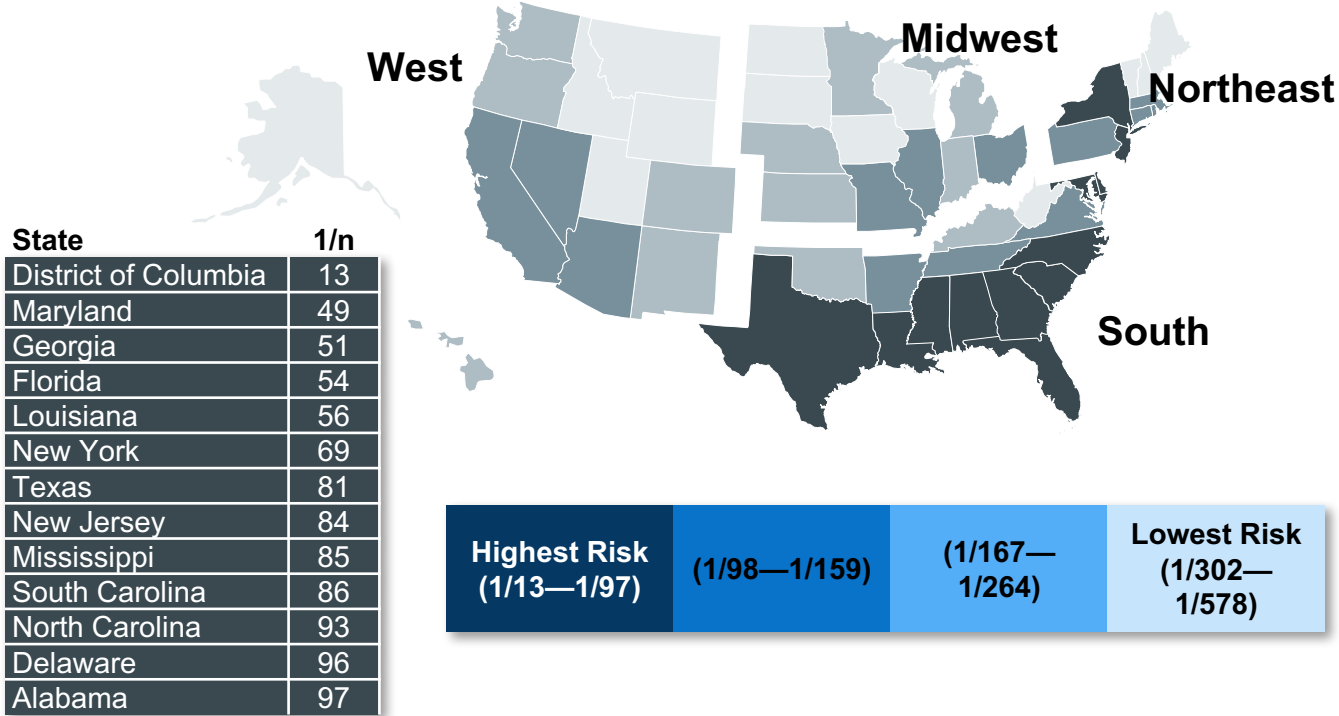
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^a Hispanics/Latinos can be of any race.

^b Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

^c Includes blood transfusion, perinatal exposure, and risk factor not reported or not identified.

Geographic Disparities in Lifetime Risk of HIV Diagnosis in the US



Source: CDC 23 Feb 2016.

Case continued

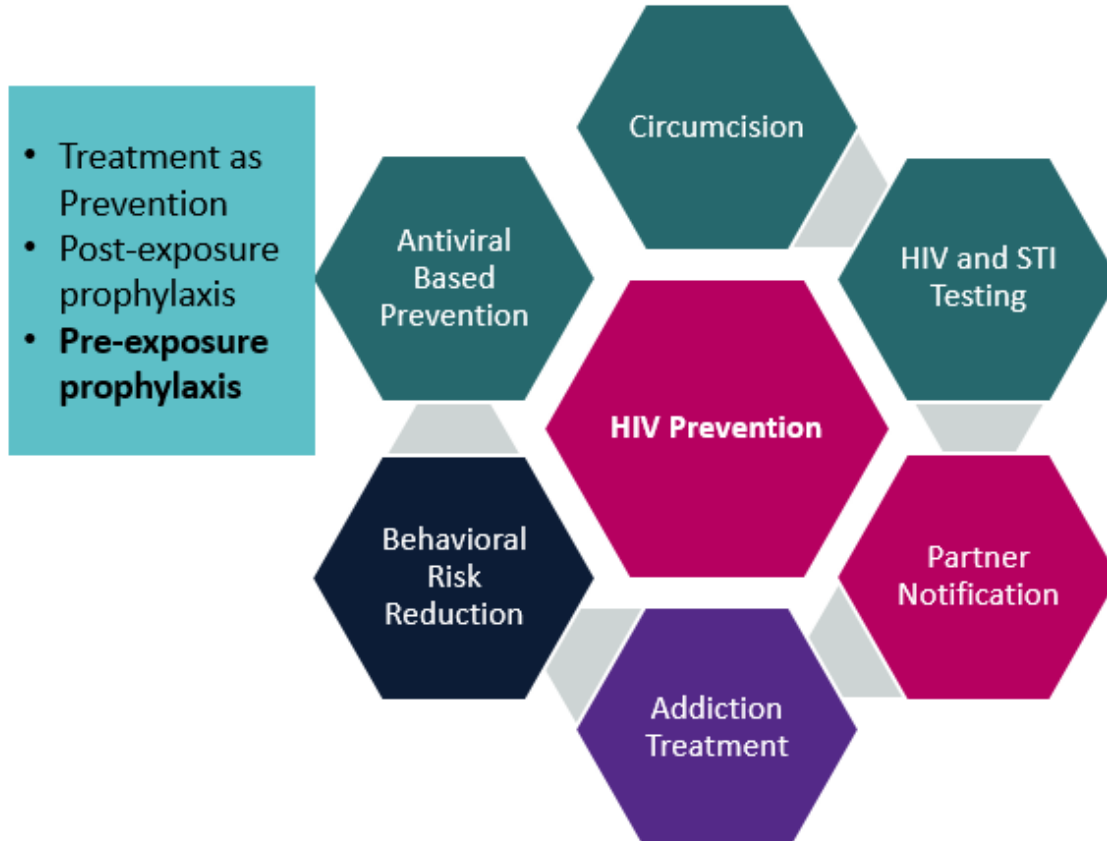
- You think about Karen's risk of HIV and remember hearing about pre-exposure prophylaxis (PrEP) for HIV prevention
- You wonder if women are using it and how well it works....

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PrEP: A new addition to the HIV prevention toolkit



What is PrEP?

- Pre-Exposure Prophylaxis is a new HIV prevention strategy in which an HIV-uninfected individual takes antiretroviral medication *before* a potential HIV exposure to prevent infection.
- Does this idea of PrEP sound familiar?

Women take birth control pills prior to intercourse to prevent pregnancy



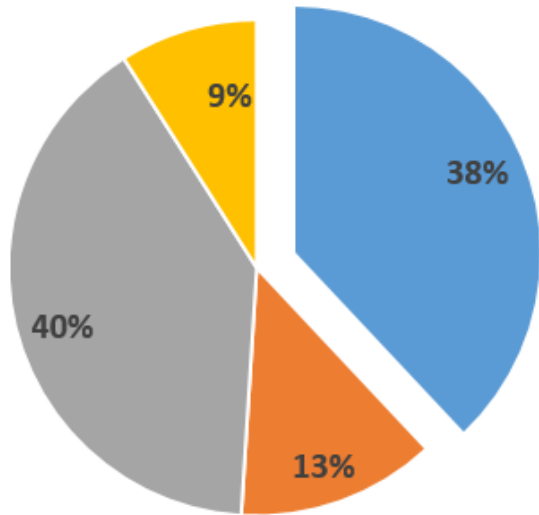
What is PrEP?

- Emtricitabine/tenofovir disoproxil fumarate (Truvada®)
 - Approved by the FDA in 2012 for PrEP
- Why emtricitabine/tenofovir for PrEP?
 - Potent: Broad and effective activity, rapidly active
 - Easy: One pill, once a day
 - Safe: Favorable safety and tolerability profiles
 - Efficacy shown in clinical studies



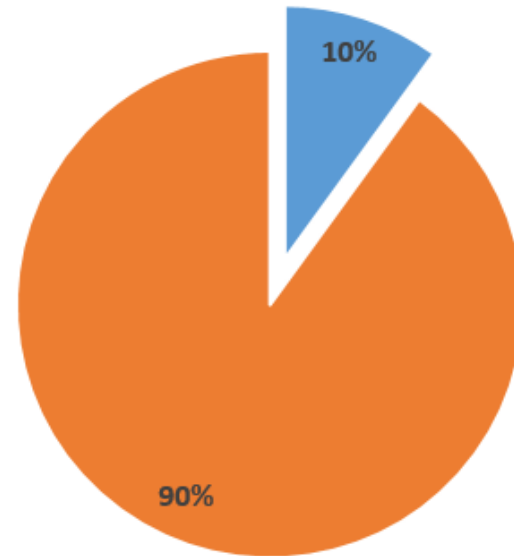
PrEP is underutilized among women

Proportion of the estimated 1.2 million individuals with PrEP indications in the U.S.



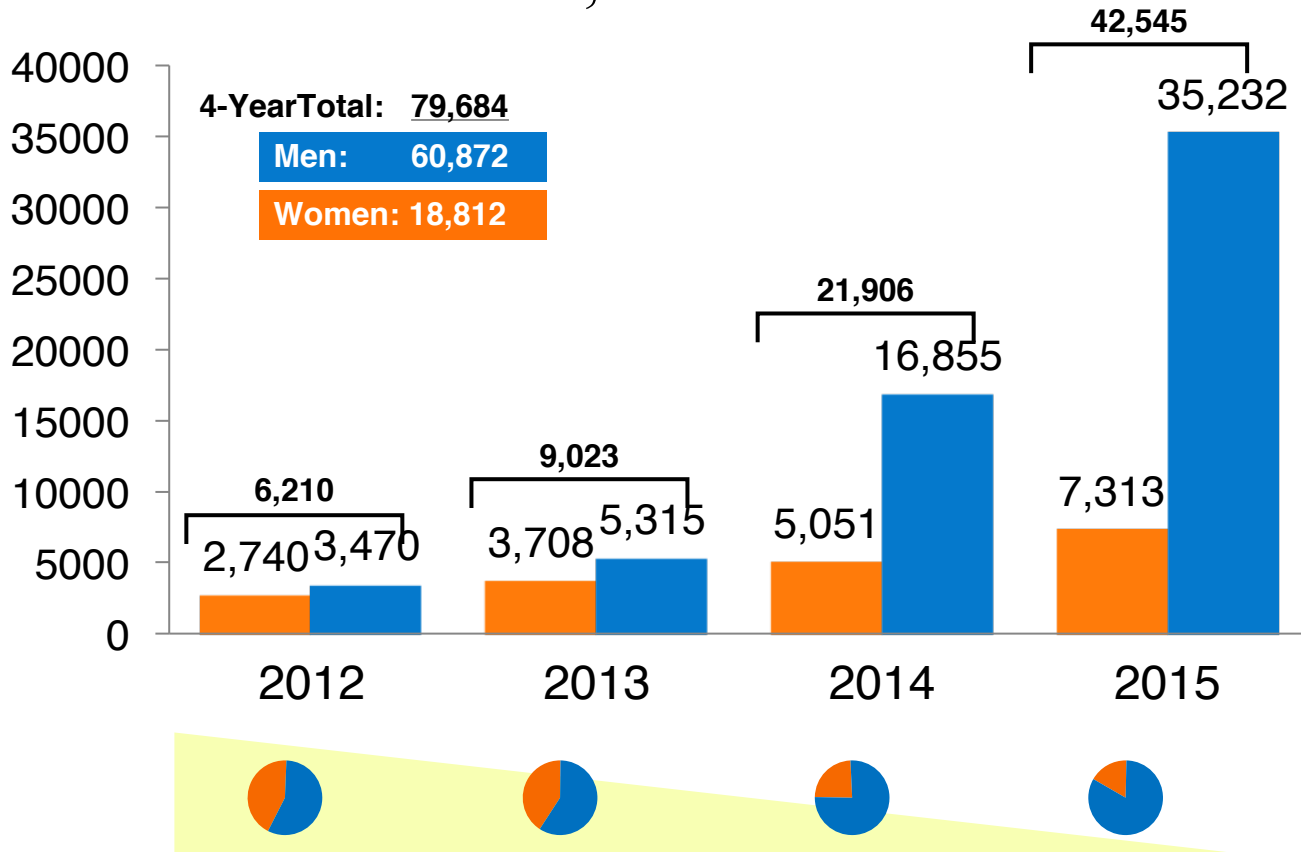
■ Heterosexual women ■ Heterosexual men ■ MSM ■ PWID

PrEP users in the U.S. (Q12016-Q32016)

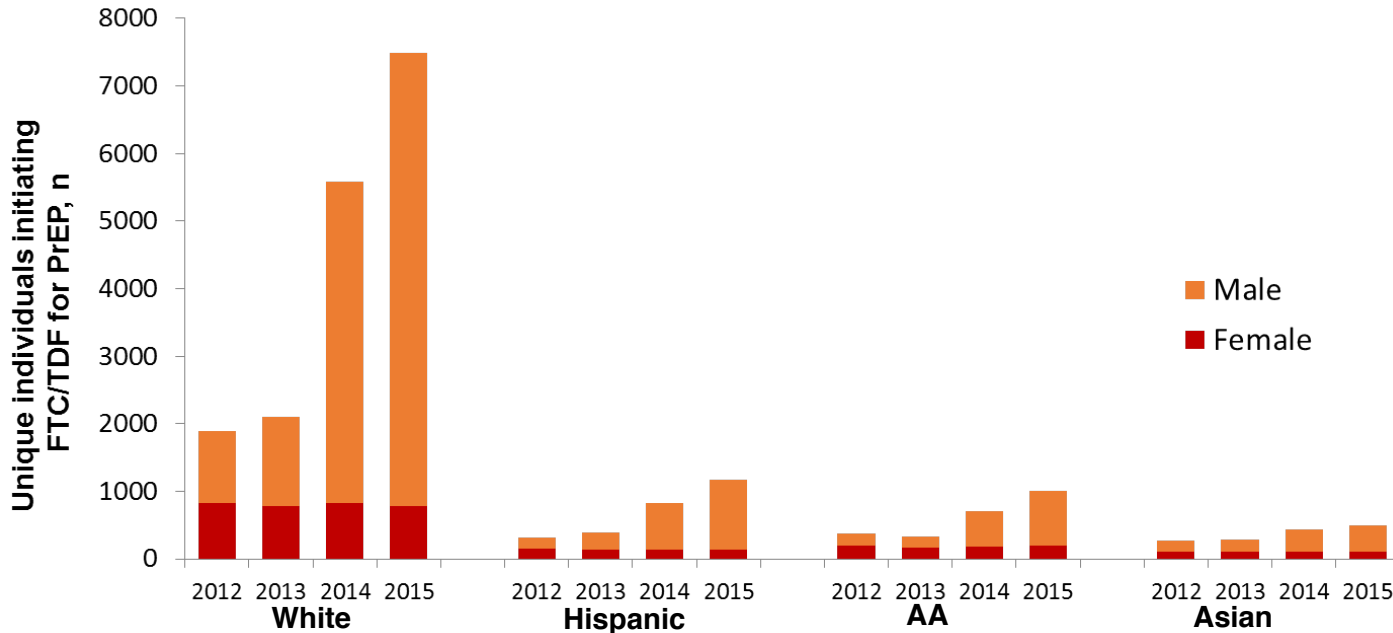


■ Women ■ Men

Gender/sex differences in new PrEP starts in US, 2012-2015



Differences in PrEP Starts by Race/Ethnicity and Sex/Gender*



* These data represent 43.7% (n=21,463) of unique individuals who have started FTC/TDF for PrEP from 2012-3Q2015 .

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PrEP Clinical Trials which included HIV-uninfected cisgender heterosexual women

Study characteristics				Benefits of PrEP (95% CI)		
Name	Study population	Sample Size	Oral PrEP agent	Plasma TDF in a random sample of participants, %	Overall efficacy	Female subgroup efficacy
Partners PrEP	Heterosexual serodiscordant couples	4747 couples (1785 in which female partner HIV-uninfected)	TDF-FTC	81%	75% (55-87%)	66% (28-84%)
			TDF	83%	67% (44-81%)	71% (37-87%)
TDF2	Heterosexual women & men	1219 (557 women)	TDF-FTC	79%	62% (22-83%)	49% (-22-81%)
BTS	People who inject drugs	2413 (489 women)	TDF	67%	49% (10-72%)	79% (17-97%)
FEM-PrEP	Heterosexual women	2120 women	TDF-FTC	24%	6% (-52-41%)	NA
VOICE	Heterosexual women	3019 women	TDF-FTC	29%	-4% (-49%-27%)	NA
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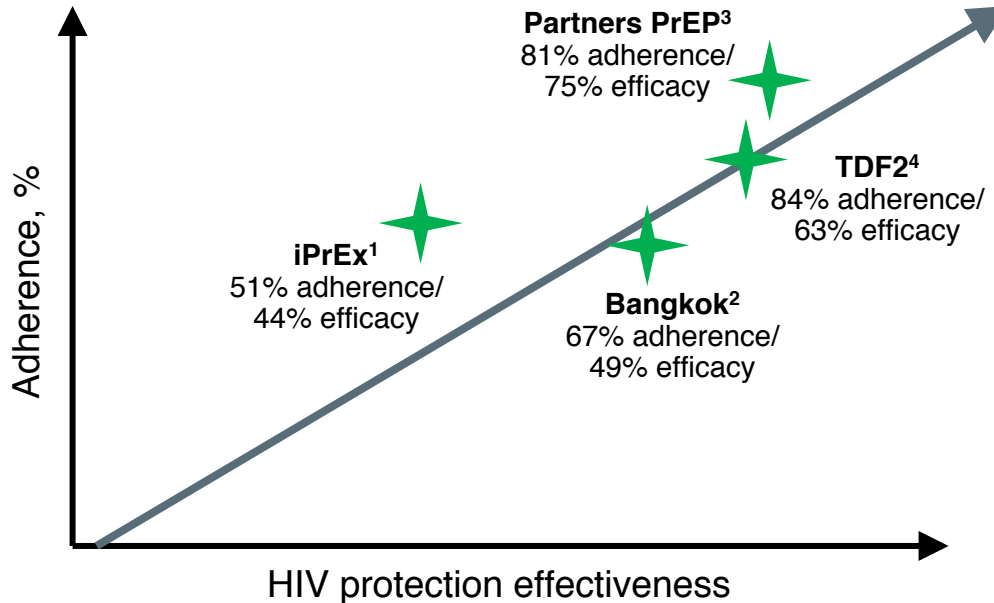
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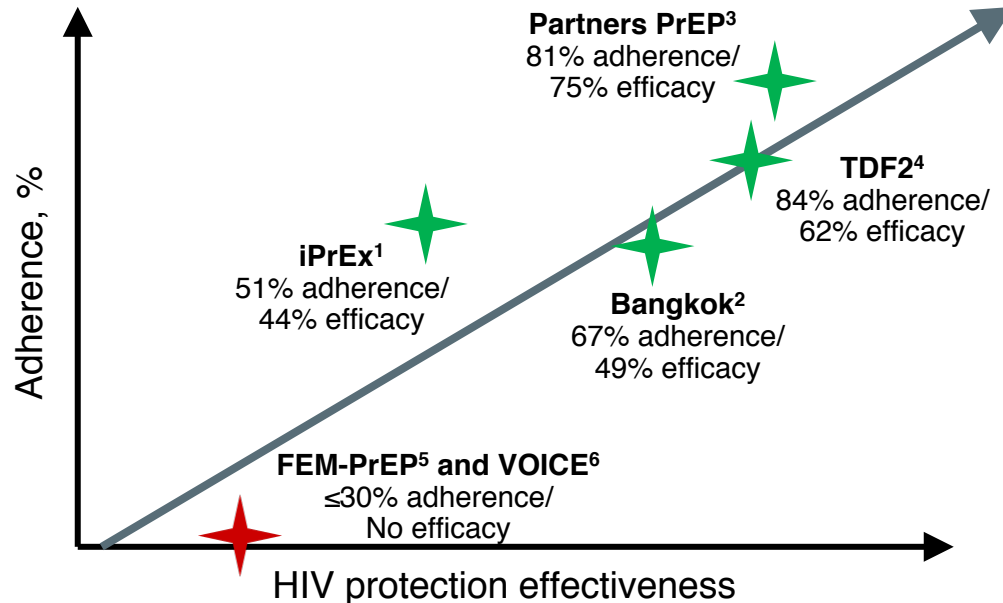
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PrEP: Better Adherence Correlates with Higher Efficacy



Trials where the majority of participants were adherent demonstrated HIV protection, with higher protection estimates when more of the population was adherent

PrEP: Low Adherence Correlates with Poor Efficacy



Trials where only a minority of participants were adherent did not/could not demonstrate HIV protection

Why was there suboptimal adherence in VOICE & FEM-PRÉP studies?

Individual

- Low perceived risk
- Concerns about side effects
- Challenges of taking a pill daily



Social/structural

- Stigma of taking a pill related to HIV

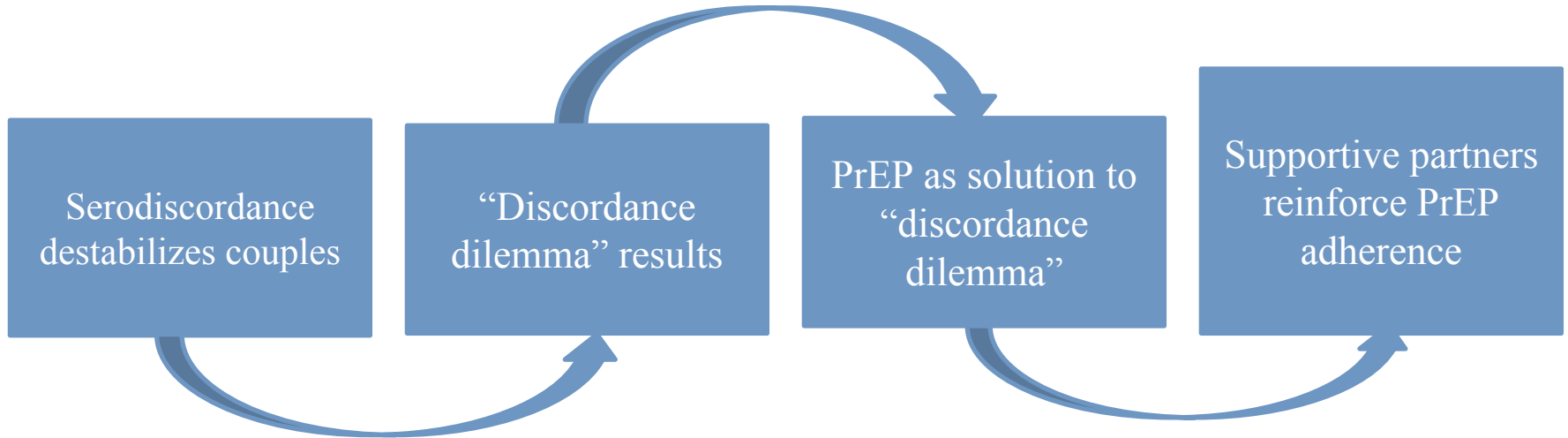
Organizational/Research

- Unknown efficacy & ambivalence towards research

Partner/Community

- Lack of support from partners & family
- Taking HIV medication for prevention?

Partners PrEP: “What’s love got to do with it [PrEP adherence]?”

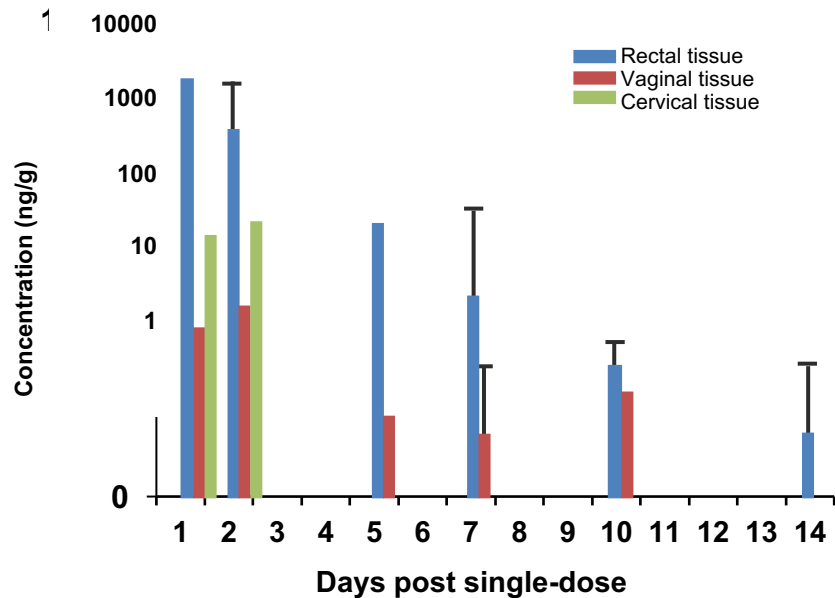


Why such divergent results in PrEP studies?

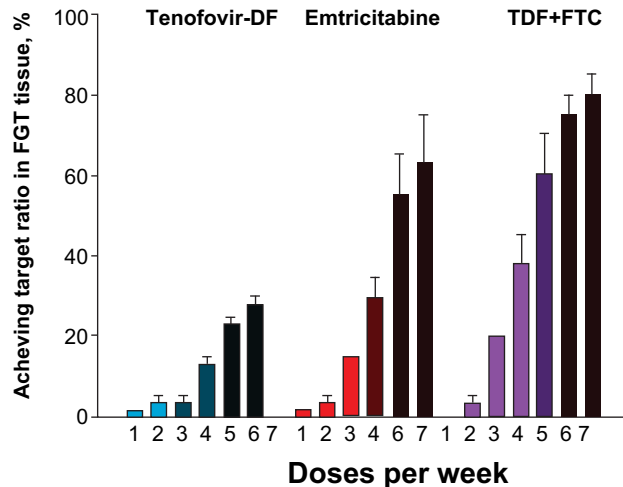
- Adherence
- **Pharmacokinetics of the genital tract**

Pharmacokinetic Differences in Various Mucosal Tissues

TFV concentrates 10-100X more in rectal tissue than in cervicovaginal tissue



Minimally effective use for FGT tissue exposure= 7 doses/week



PrEP Effectiveness Is Associated With Drug Concentration

Route of HIV exposure	Drug concentration commensurate with doses	HIV risk reduction (95 % CI)
Rectal tissues	2 per week	76% (56%-96%)
	4 per week	96% (90%-99%)
	7 per week	99% (96%-99%)
Vaginal/cervical tissues	6-7 per week	94% (-17%-100%)

Cottrell ML, et al. AIDS Res Hum Retroviruses. 2014;30:A60;
Donnell D, et al. J Acquir Immune Defic Syndr. 2014;66:340-8.
Anderson PL, et al. Sci Transl Med. 2012;4:151ra125.
Cottrell ML. et al. J Infectious Dis. 2016; 214:55-64

Why such divergent results in PrEP studies?

- **Adherence**
- **Pharmacokinetics of the genital tract**

****PrEP works for women if taken daily**

Safety

- Side effects are mild and usually temporary
 - Most common: nausea, cramping, unintended weight loss
 - Occur in the first few weeks of treatment
 - Quickly subside
 - Other observed side effects
 - Bone mineral density and renal function: small, but statistically significant declines
 - Levels off over time and does not progress
 - Resolves after stopping medication

Case continued

- Karen mentions that she is thinking about trying to get pregnant, but she's not sure
- You wonder about the safety and efficacy of PrEP in women who are trying to conceive as well as those who might be pregnant or breastfeeding

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- Epidemiology of HIV in U.S. women
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HIV risk during the periconception period, pregnancy & breastfeeding



- HIV-negative women are at substantial risk of acquiring HIV during attempts to conceive with HIV-positive male partner
- Pregnancy may be associated with an increased risk of HIV acquisition
- Acute HIV in pregnancy associated with 3 to 6 times increased risk of perinatal transmission
- Acute HIV in breastfeeding associated with 4 to 5 times increased risk of neonatal transmission

PrEP efficacy and safety during the periconception period, pregnancy & breastfeeding

- Very limited data available
- Women who were pregnant, breastfeeding, or intended to get pregnant were excluded
- Contraception required for study enrollment
- PrEP was discontinued in women who became pregnant



PrEP-ception: safety



FOUNDATIONS 30
OF CHICAGO

- Partners PrEP study
 - PrEP discontinued when pregnancy detected
 - Mean in utero exposure to PrEP about 5 weeks
- No significant differences in pregnancy incidence, birth outcomes, and infant growth
- “Signal” for PrEP associated with pregnancy loss?
 - 42.5% for TDF-FTC vs. 32.3% for placebo
(difference 10.2%; 95% CI, -5.3% (protective) to 25.7% (harmful);
 $p = 0.16$)

PrEP's efficacy during the periconception period

- Studies ongoing, but complete data not yet available
- Small observational studies of serodiscordant couples
- Timed intercourse in combination with PrEP in couples with a HIV-negative female partner and a virally suppressed HIV-positive male partner → no HIV transmissions

Prevention options for HIV-negative women in serodiscordant partnerships seeking to conceive

- One or more (ideally the latter) of the following options in combination:
 - Antiretroviral treatment of the HIV-positive male partner to achieve an undetectable viral load
 - STI diagnosis and any indicated treatment for both partners before conception attempts
 - **Daily oral PrEP beginning 1 month before a conception attempt and continuing for 1 month after a conception attempt**
 - Intravaginal or intrauterine insemination, or intracytoplasmic sperm injection with a semen sample processed by “sperm washing”
 - Limit sex without a condom to peak fertility times

TDF/FTC in Pregnancy



- Limited data
- Overall TDF appears safe during pregnancy
 - No increased risk of growth or bone abnormalities in exposed infants
- Needed: prospective data from studies with bone mineral density measurements; randomized controlled design, and long term safety data

Teratogenicity among HIV-positive women on TDF- and FTC-containing regimen

HIV-Positive Women on ART	Any FTC-Containing Regimen ¹	Any Tenofovir-Containing Regimen ¹
Pregnancies enrolled, n		
First trimester	1728	2478
Second trimester	525	670
Third trimester	206	351
Defects/live births, n/n (%)		
First trimester exposure	35/1543 (2.3%)	47/2141 (2.2%)
Second/third trimester exposure	15/729 (2.1%)	21/1021 (2.1%)

- Among pregnant women in the US reference population, the background rate of birth defects is 2.7%.
- There was no association between FTC or tenofovir and overall birth defects observed in the APR^{1,2}

¹ Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2014. Wilmington, NC: Registry Coordinating Center; 2014. <http://www.APRegistry.com> ² TRUVADA US Prescribing Information. Gilead Sciences, Inc. 2013. Courtesy: Staci Bush

TDF/FTC during lactation



- Limited data
- TDF/FTC promoted for HIV-infected lactating women by the WHO in low-resource settings
- TDF/FTC is secreted in breast milk, but infant levels are extremely low (<2% proposed infant doses)

PrEP and Hormonal Contraception

- No difference in PrEP's efficacy
 - among women using injectable depot medroxyprogesterone acetate (DMPA) vs. DMPA non-users
 - For men whose female partners used DMPA vs. those with partners who did not
- No change in contraceptive efficacy in women using PrEP and combination oral contraceptives, injectables, and implants



Case continued

- You've now familiarized yourself with available PrEP safety and effectiveness data
- You think Karen may be an appropriate candidate for PrEP and decide to conduct a PrEP eligibility assessment

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Obtaining a sexual history

“The best sexual history focuses on *theme* not plot”

- How/What Method

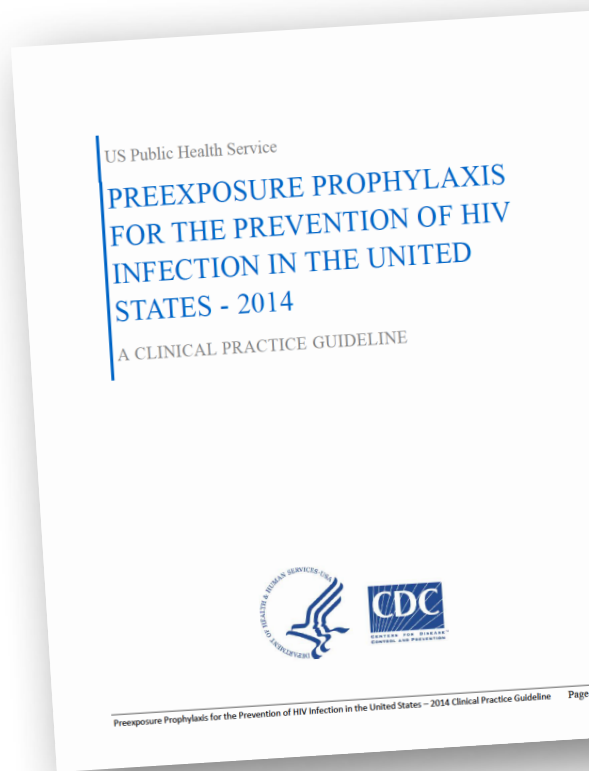
How would you describe your sex life?

What do you think about your risk for HIV?

How well are you taking care of your sexual health right now?

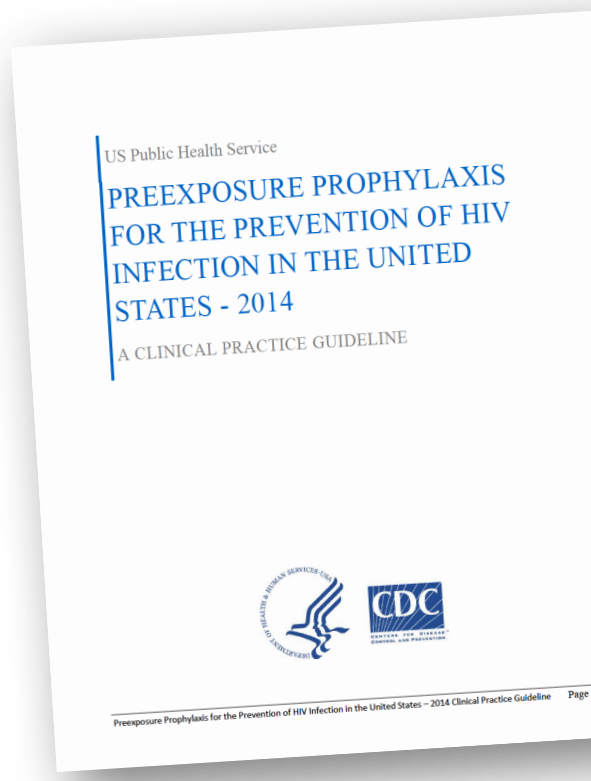
What could you do to take better care of your sexual health?

Guidance for PrEP indications





- HIV uninfected, plus:
- Any HIV-positive partner(s)
 - Condomless sex in past 6 months
 - Any STI in past 6 months
 - High number of sex partners
 - In high-prevalence area or sexual network
 - Commercial sex work
 - Shared injection equipment
 - Recent drug treatment and current relapse

Guidance for PrEP indications



US Public Health Service
**PREEXPOSURE PROPHYLAXIS
FOR THE PREVENTION OF HIV
INFECTION IN THE UNITED
STATES - 2014**
A CLINICAL PRACTICE GUIDELINE

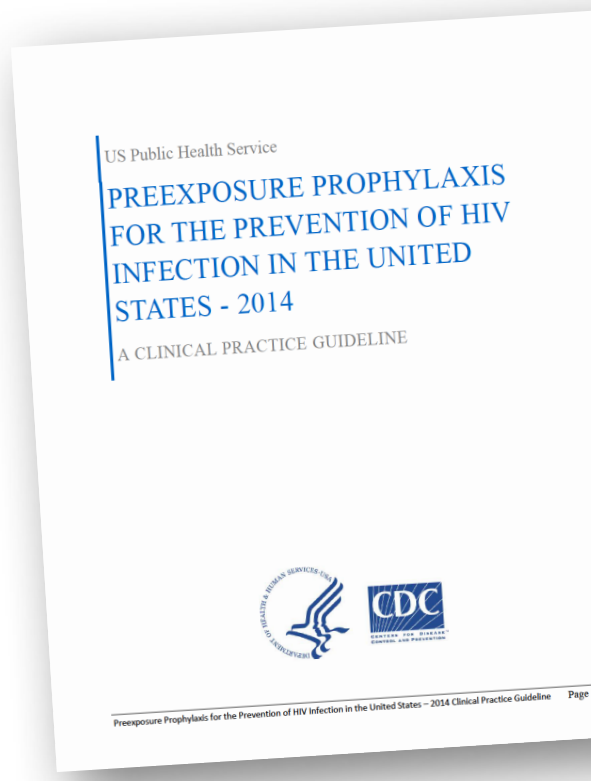
 

Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline Page



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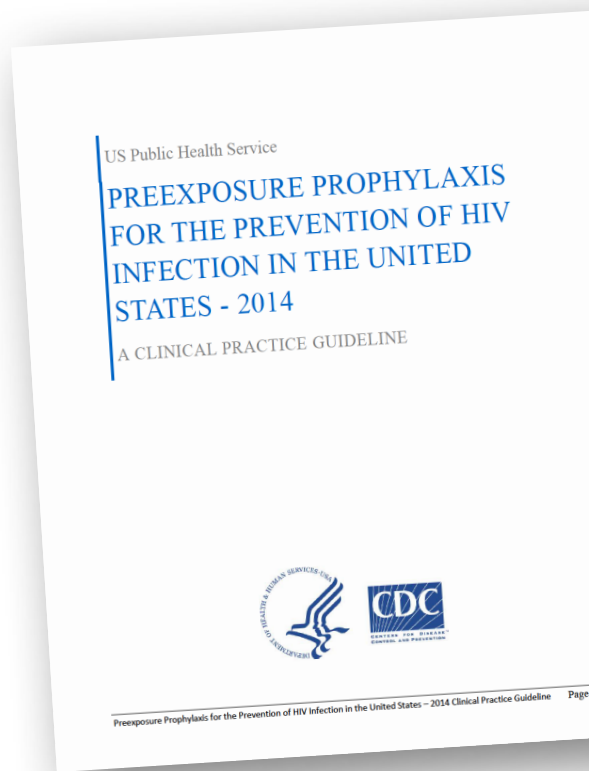
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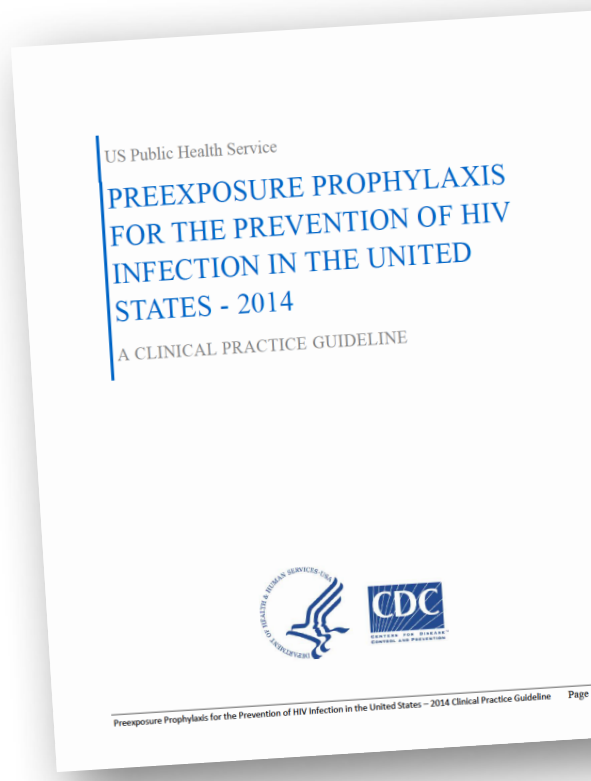
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Guidance for PrEP indications



The image shows the cover of a clinical practice guideline document. The title is 'PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014' in blue text. Below the title, it says 'A CLINICAL PRACTICE GUIDELINE'. At the bottom, there are logos for the Department of Health and Human Services and the CDC. The page number 'Page' is visible at the bottom right of the cover.

US Public Health Service

PREEXPOSURE PROPHYLAXIS
FOR THE PREVENTION OF HIV
INFECTION IN THE UNITED
STATES - 2014

A CLINICAL PRACTICE GUIDELINE

DEPARTMENT OF HEALTH & HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

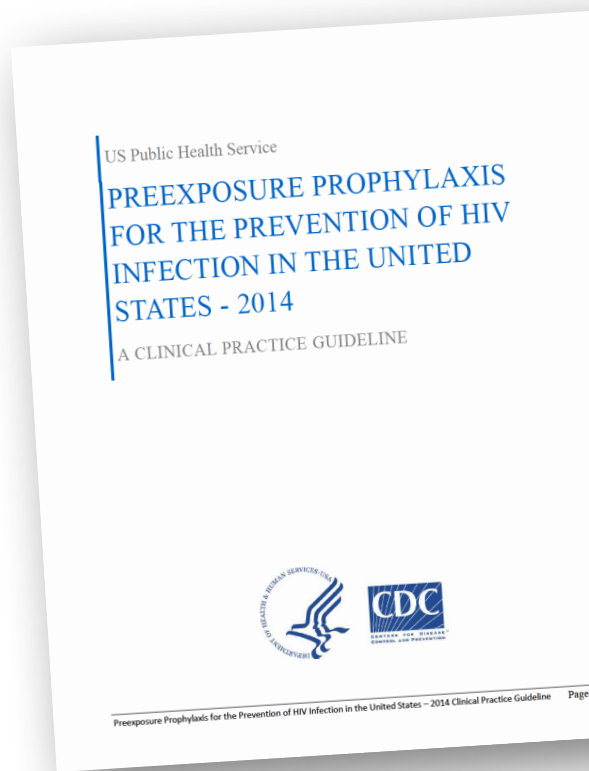
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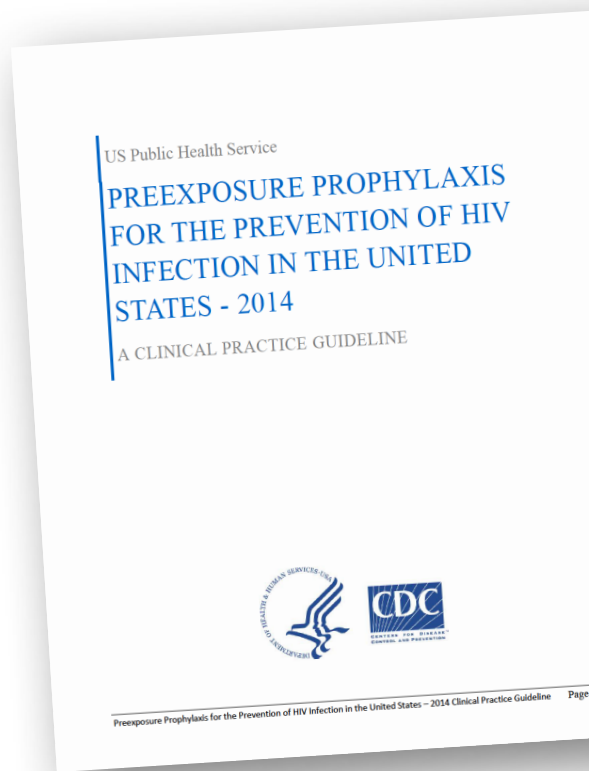
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 - Any STI in past 6 months
 - High number of sex partners
 - **In high-prevalence area or sexual network**
 - Commercial sex work
 - Shared injection equipment
 - Recent drug treatment and current relapse

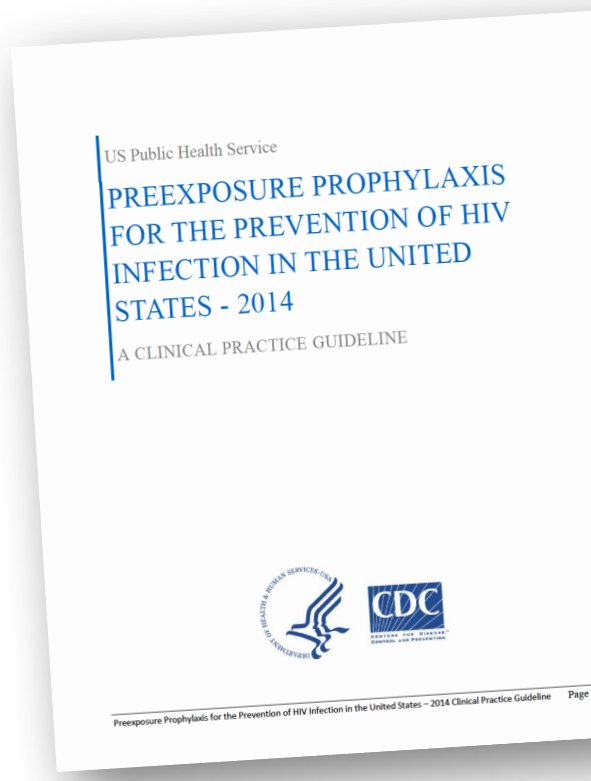
Guidance for PrEP indications



HIV uninfected, plus:

- Any HIV-positive partner(s)
- Condomless sex in past 6 months
- Any STI in past 6 months
- High number of sex partners
 - In high-prevalence area or sexual network
 - **Commercial sex work**
- Shared injection equipment
- Recent drug treatment and current relapse

Guidance for PrEP indications



The image shows the cover of a clinical practice guideline document. The title is 'PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014' in blue text. Below the title, it says 'A CLINICAL PRACTICE GUIDELINE'. At the bottom, there are logos for the Department of Health and Human Services and the CDC. The text 'US Public Health Service' is at the top left. At the bottom right, it says 'Page'.

US Public Health Service

**PREEXPOSURE PROPHYLAXIS
FOR THE PREVENTION OF HIV
INFECTION IN THE UNITED
STATES - 2014**

A CLINICAL PRACTICE GUIDELINE

DEPARTMENT OF HEALTH & HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline Page

- HIV uninfected, plus:
 - Any HIV-positive partner(s)
 - Condomless sex in past 6 months
 - Any STI in past 6 months
 - High number of sex partners
 - In high-prevalence area or sexual network
 - Commercial sex work
 - **Shared injection equipment**
 - **Recent drug treatment and current relapse**

Other indications for PrEP in women?

- Any HIV-negative woman who:
 - Uses stimulant drugs associated with high-risk behaviors
 - Has been prescribed nPEP and demonstrates continued high-risk behavior OR have used multiple courses nPEP
 - Has experienced intimate partner violence
 - Reports transactional sex

Baseline Evaluation & Prescribing

A. Determine eligibility

- Substantial ongoing risk for HIV
- Ready to take a pill daily and return every 3 months
- Screen for HIV and consider need for HIV RNA
- Screen for STIs, Hepatitis B serologies, renal function & pregnancy

Baseline Evaluation & Prescribing

- Currently using contraception?
- If not, interested in contraception in addition to condoms?
- Trying to conceive?
- Currently pregnant?
- Currently breastfeeding?

Baseline Evaluation & Prescribing

A. Determine eligibility

- Substantial ongoing risk for HIV
- Ready to take a pill daily and return every 3 months
- Screen for HIV and consider need for HIV RNA
- Screen for STIs, Hepatitis B serologies, renal function & pregnancy

B. Prescribing

- Emtricitabine/tenofovir 1 tab po daily
- No more than 90-day supply at a time
- Emphasize importance of adherence

***Differences in time to “protection”
after PrEP initiation**

Cervico-vaginal tissues						
		①	②	③	④	⑤
⑥	⑦	⑧	⑨	⑩	⑪	⑫
⑬	⑭	⑮	⑯	⑰	⑱	⑲
⑳						

20 days

Rectal tissues						
		①	②	③	④	⑤
⑥	⑦					

7 days

Counseling & Monitoring

C. Continue Counseling

- Continue risk reduction counseling and other preventive/ harm reduction measures and discussion of reproductive plans

D. Lab monitoring

- Every 3 month HIV and pregnancy tests
- Every 3-6 month STI screening
- Renal function at 3 months, then every 6 months thereafter

Antiretroviral Pregnancy Registry

***THE
ANTIRETROVIRAL
PREGNANCY
REGISTRY***

[Home](#)
[Disclaimer](#)
[Privacy Policy](#)

The Antiretroviral Pregnancy Registry enrolls patients through their health care provider. For information on the Registry and related information follow the "Health Care Providers" link. If you are a patient interested in learning about the Registry or other related information or sites, follow the "Patients" link below:

[Patients](#) [Health Care Providers](#)

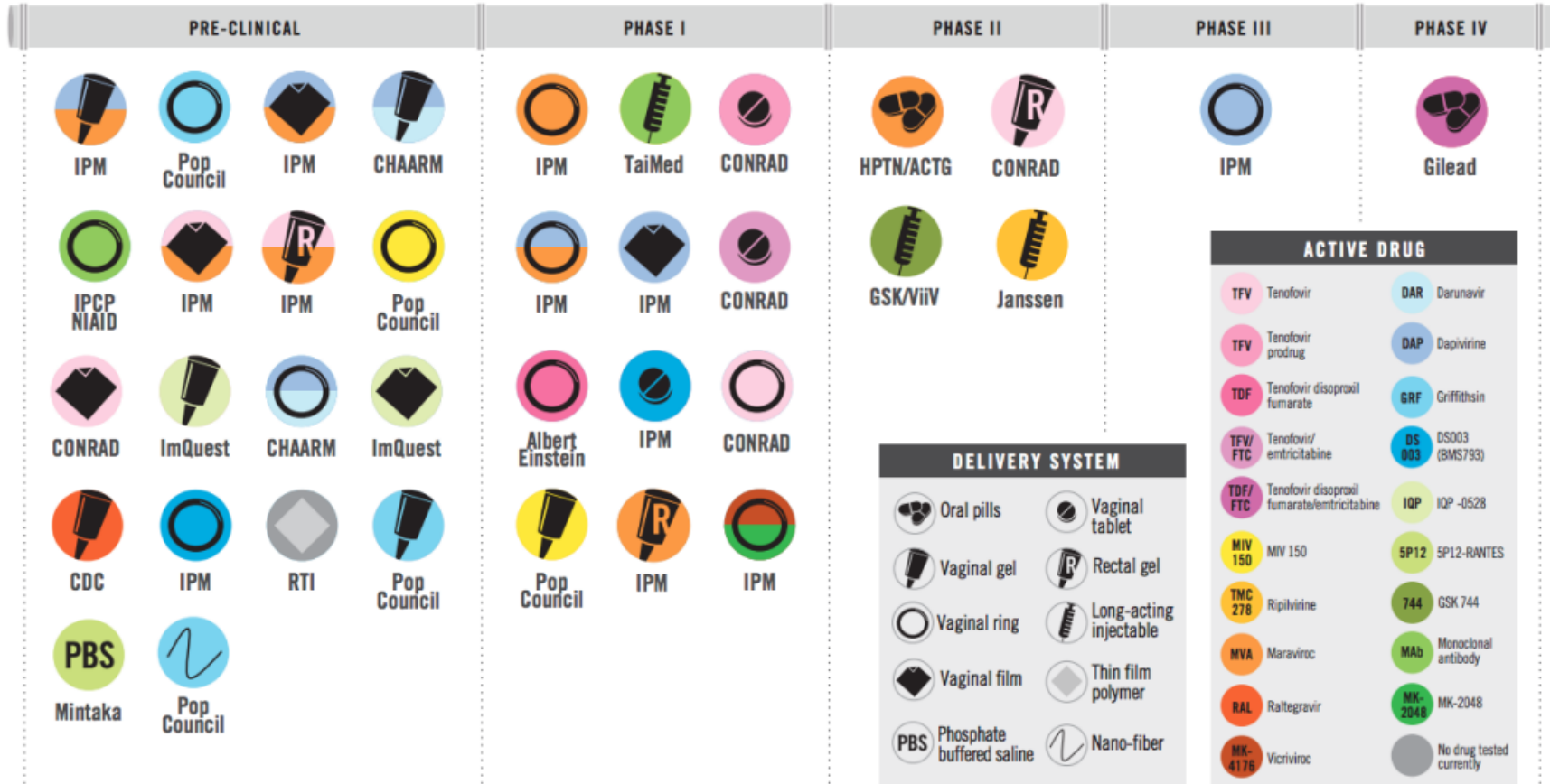
The success of the Registry depends on the continued participation of health care providers who register patients and assist in providing follow-up information postpartum. The support and participation of providers who enroll and continue to enroll patients are greatly appreciated.

www.apregistry.com

Case continued...

- Karen has been using a vaginal ring for contraception and wonders if something similar is available for PrEP

PrEP pipeline



Vaginal ring for HIV prevention: advantages & considerations

- Long acting: Monthly or longer
- Easy to use, comfortable
- Suitable for a wide range of
- Potential for drug combinations



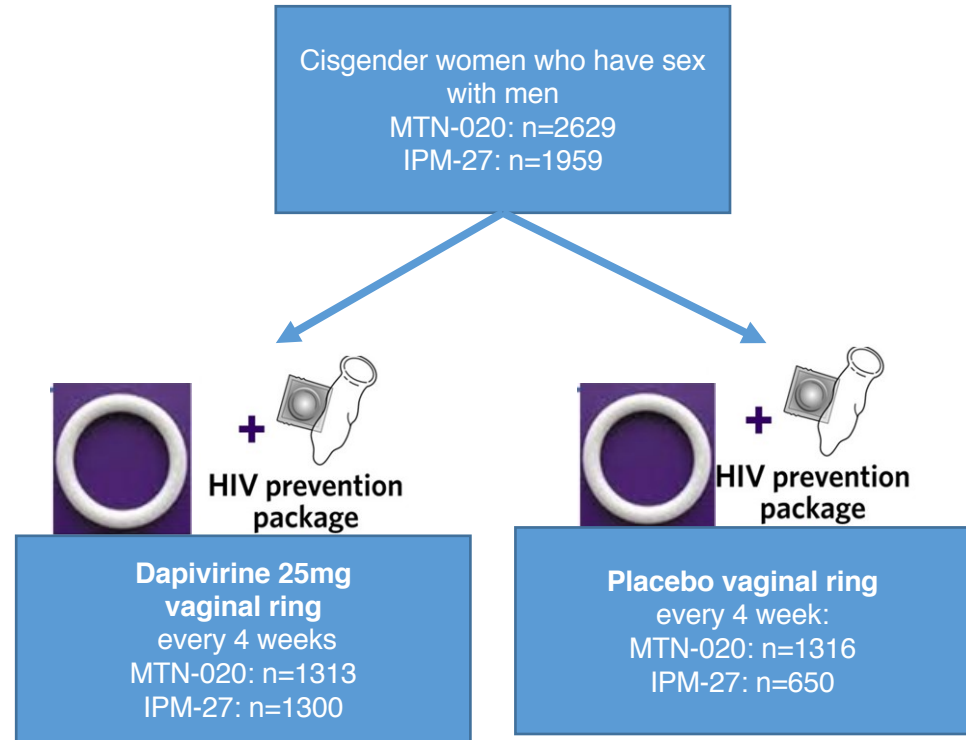
Dapivirine vaginal ring

- Highly potent non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Flexible silicone ring
- Designed for 4-week use
- Slowly releases dapivirine when inserted in the vagina



Efficacy & safety of the dapivirine vaginal ring

- Two randomized, double-blind, placebo-controlled Phase III **efficacy & safety** trials of dapivirine vaginal ring for HIV prevention in women



Efficacy & safety of the dapivirine vaginal ring

	MTN-020 ¹ (15 sites)		MTN-020 ¹ (13 sites)*		IPM-27 ² (7 sites)	
	Dapivirine (n=1308)	Placebo (n=1306)	Dapvirine (n=1198)	Placebo (n=1197)	Dapivirine (n=1300)	Placebo (n=650)
HIV-1 incidence (per 100 p-y)	3.3	4.5	2.8	4.4	4.1	6.1
Risk reduction (relative to placebo) (95% CI)	27% (1, 46)		37% (12, 56)		31% (12, 56)	

*excludes two sites with lower than expected protocol and product adherence

- No difference in safety endpoints between the study arms

Dapivirine vaginal ring: Differences in risk reduction by adherence level

	Placebo arm	Non-Adherent (≥ 23.5 mg)	Low to high (<23.5mg)	Medium to high (<22 mg)
# HIV-1 Infections	50	13	14	7
HIV-1 incidence (per 100 p-y)	4.6	3.6	1.9	1.5
Risk reduction (relative to placebo) (95% CI)	--	31% (-28, 63)	56% (20, 76)	65% (22,84)

Case concludes...

- You explain to your patient that there may be some newer options in the future, but, as of now, a daily pill is the only option
- After more discussion, together, you decide that she will start daily oral PrEP....

Coverage for PrEP care and medication



1. Gilead Advancing Access Co-pay Card
www.gileadadvancingaccess.com
2. Patient Advocate Foundation (PAF)
www.copays.org
3. Patient Access Network Foundation
panfoundation.org

1. Enroll in an insurance marketplace
www.healthcare.gov
2. Check Medicaid eligibility
www.medicaid.gov
3. Find a FQHC and enroll patient in the Gilead MAP
www.truvada.com/truvada-patient-assistance

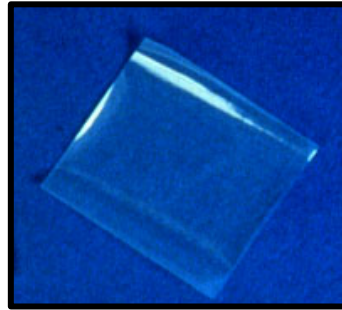
Take home points

- PrEP works in women if taken (daily)
- Limited data exists about PrEP's safety and efficacy in the context of reproductive health, but existing data appears reassuring
- Appropriate candidates for PrEP include women who report continued high risk exposure (individual, partner-level, & community-level)
- Discuss women's reproductive plans and provide counseling and adherence support

Women need effective user-controlled HIV prevention options



Gel



**Vaginal
film**



Pill



**Vaginal
ring**



Injectable



PrEP may not be for EVERY woman,
but it's an option for ALL women

-Kimberleigh Smith, MPA,
Callen-Lorde

Questions



Feel free to email me at:
oblackst@montefiore.org

Table 4. Annual and 10-year probability of HIV transmission in couple with an HIV-positive male and an HIV-negative female partner with varying combinations of risk modifiers.

Scenario ^a	Cumulative probability of HIV transmission	
	1 year	10 years
Receptive anal sex (RAS)	20%	89%
PrEP and RAS	10%	66%
Base case – vaginal sex only, no anal sex	6%	44%
Condoms and RAS	4%	35%
Condoms and PrEP and RAS	4%	35%
Preexposure prophylaxis (PrEP)	2%	15%
Consistent condom use (condoms)	1%	11%
ART and RAS	0.9%	8%
Condoms and PrEP	0.3%	3%
Antiretroviral therapy for positive partner (ART)	0.2%	2%
ART and PrEP	0.1%	1%
ART and condoms	0.05%	0.5%
ART and condoms and PrEP	0.05%	0.5%

^aUnless otherwise specified, scenarios assume 6 acts of receptive vaginal sex per month. Scenarios with RAS assume 1 act of receptive anal sex and 5 acts of receptive vaginal sex per month.

Efficacy & safety of the dapivirine vaginal ring

	MTN-020¹ (15 sites)		MTN-020¹ (13 sites)*		IPM-27² (7 sites)	
	Dapivirine (n=1308)	Placebo (n=1306)	Dapvirine (n=1198)	Placebo (n=1197)	Dapivirine (n=1300)	Placebo (n=650)
# HIV-1 infections	71	97	54	85	77	56
HIV-1 incidence (per 100 p-y)	3.3	4.5	2.8	4.4	4.1	6.1
Risk reduction (relative to placebo) (95% CI), p-value	27% (1, 46) P=0.046		37% (12, 56) P=0.007		31% (12, 56) P=0.007	
Among women older than 21 y.o.	---		56% (31, 71) (p<0.001)		37.5% (3.5, 59.5) (p=0.10)	

- No difference in safety endpoints between the study arms

*excludes two sites with lower than expected protocol and product adherence

Dapivirine vaginal ring: Differences in risk reduction by adherence level

	Placebo arm	Non-Adherent (≥ 23.5 mg)	Low to high (< 23.5 mg)	Medium to high (< 22 mg)
# HIV-1 Infections	50	13	14	7
HIV-1 incidence (per 100 p-y)	4.6	3.6	1.9	1.5
Risk reduction (relative to placebo) (95% CI), p-value	--	31% (-28, 63) p=0.24	56% (20, 76) p=0.007	65% (22, 84) p=0.01

PrEP in real world clinical practice

- Retrospective chart review of two urban U.S. medical centers
- Women at high risk of HIV preconception, during pregnancy and lactation referred to specialty clinics
- 67% of those offered PrEP chose to use PrEP (n=27)
- 26/27 had a male partner who has HIV-positive, 42% with undetectable viral load
- Median time on PrEP: 30 weeks (range: 4-74)
- 50% reported challenges with adherence
- 57% in care at delivery had no postpartum follow-up